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Copper(II)-catalyzed three-component coupling sequence for the efficient synthesis of 2-arylquinolines: 1,4-dioxane serving as the C_2 building block

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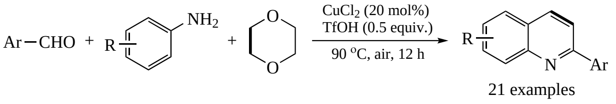
A copper-catalyzed three-component coupling sequence for 2-arylquinolines formation from aromatic aldehydes, anilines and 1,4-dioxane has been described. Unexpectedly, 1,4-dioxane served as a C_2 building block in this transformation. This formal [4 + 2] approach provides rapid access to 2-arylquinolines with broad substrate scope under mild conditions.



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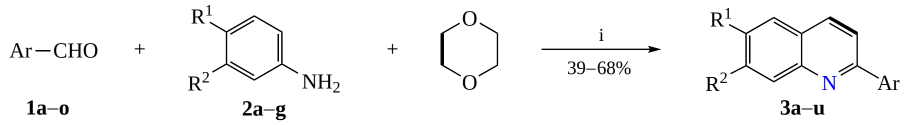
Quinoline and their derivatives belong to extremely important heterocycles which are found in pharmaceuticals and bioactive natural products.[1–3] Among them, 2-arylquinoline scaffolds are much attractive for their useful properties.[4–7] Considering their importance, much effort has been made for their synthesis, and a variety of facile procedures has been disclosed.[8,9] Jiang reported Pd-catalyzed annulation of benzaldehyde, aniline and acrylic acid followed by decarboxylation affording 2-substituted and 2,3-disubstituted quinolines.[10] Larsen demonstrated the construction of alkyl-substituted quinolines by Cu-catalyzed three-component reaction of readily available anilines, aldehydes, and alkynes.[11] Alternatively, Ma described the Rh-catalyzed double C−H alkenylation of *N*-arylmethanimines toward 2-aryl-quinolines using ethene-1,2-diyl carbonate as a vinylene unit.[12] Despite of these achievements, further development of more facile and general approaches towards 2-arylquinolines from commercial available materials under mild conditions is still in high demand.

On the other hand, 1,4-dioxane and its derivatives represent an important basic chemical feedstock and widely used solvents.[13] It is known that the $C(sp^3)$–H bonds adjacent to oxygen atoms have a relatively lower bond dissociation energy, which indicates that homolytic cleavage of these C–H bonds should easily take place under oxidative conditions.[14] For instance, Ji and other groups reported that 1,4-dioxane served as a C_1 building-block with the peroxide assistance in some reactions.[15] Liu disclosed Cu catalyzed oxidative cleavage of the $C(sp^3)$–$C(sp^3)$ bond of 1,4-dioxane for the synthesis of acyloxy ethers and their derivatives.[16] However, as compared to the direct functionalization of $C(sp^3)$H bond adjacent to the oxygen atom in 1,4-dioxane, to the best of our knowledge, 1,4-dioxane has been seldom employed as a C_2 building block.[17–20] Herein, we wish to report a novel and simple method for the formation of 2-arylquinolines through the three-component reaction of aldehydes, anilines and 1,4-dioxane, with 1,4-dioxane serving as both a solvent and a C_2 building block.

We initiated our investigation on the model reaction of benzaldehyde **1a** and aniline **2a** in 1,4-dioxane to optimize the critical reaction parameters. To our delight, we found that in the presence of a catalytic amount of $Cu(OTf)_2$ under atmospheric conditions product **3a** was formed in 31% yield (Table 1, entry 1). However, when the reaction was conducted in other solvent (DMF or MeCN) no desired product could be obtained at all, which confirmed that 1,4-dioxane truly served as a C_2 source in this assembling (entries 1–3). Other catalysts such as AgOTf, $Cu(OAc)_2$ or $CuCl_2$ failed to promote the transformation (entries 4–6). Interestingly, the yield of **3a** was increased significantly to 53% when 0.5 equiv. of TfOH was added, however further raising the amount of TfOH did not have any positive effect (entry 7). Other acids such as trifluoroacetic and acetic ones were not effective (entries 7–9). Subsequently, in the presence of TfOH, other copper salts were also tested, while $CuCl_2$ appeared to be the best one delivering the desired product in 62% yield (entries 10–13). Further optimization revealed that the **1a**/**2a** molar ratio of 1 : 2 and their lower concentrations were more favorable for the reaction to proceed (entries 13, 14). Additionally, comparable yields were achieved when the reaction was carried out under oxygen atmosphere while the yield decreased dramatically under nitrogen (entry 15). In addition, lowering the amount of $CuCl_2$ resulted in the decreased yield of product **3a**, which could be attributed to the synergetic oxidative effect with O_2 (entry 16). After considerable experimentation, we found that the combination of benzaldehyde **1a** with 2 equiv. of aniline **2a** in 1,4-dioxane (4 ml) promoted by 20 mol% $CuCl_2$ and 0.5 equiv. TfOH at 90 °C under air for 12 h may be selected as optimal (see Table 1, entry 13).

Under the optimized reaction conditions, the substrate scope was screened (see Scheme 1).† As expected, almost all of the substrates reacted smoothly to provide the corresponding products **3a**–**u** in moderate to good yields. The electronic properties of the substituents on the benzene ring have slight



1a Ar = Ph
1b Ar = 4-Bu^{t}C$_6$H$_4$
1c Ar = 4-MeOC$_6$H$_4$
1d Ar = 4-FC$_6$H$_4$
1e Ar = 4-ClC$_6$H$_4$
1f Ar = 4-BrC$_6$H$_4$
1g Ar = 4-F$_3$CC$_6$H$_4$
1h Ar = 4-NCC$_6$H$_4$
1i Ar = 4-O$_2$NC$_6$H$_4$
1j Ar = 4-MeC$_6$H$_4$
1k Ar = 3-MeC$_6$H$_4$
1l Ar = 2-MeC$_6$H$_4$
1m Ar = 3-ClC$_6$H$_4$
1n Ar = 2-furyl
1o Ar = 2-naphthyl

2a R^1 = R^2 = H
2b R^1= OMe, R^2 = H
2c R^1 = R^2 = Me
2d R^1= Br, R^2 = H
2e R^1= Cl, R^2 = H
2f R^1= H, R^2 = Cl
2g R^1= Ac, R^2 = H

3a Ar = Ph, R^1 = R^2 = H
3b Ar = 4-Bu^{t}C$_6$H$_4$, R^1 = R^2 = H
3c Ar = 4-MeOC$_6$H$_4$, R^1 = R^2 = H
3d Ar = 4-FC$_6$H$_4$, R^1 = R^2 = H
3e Ar = 4-ClC$_6$H$_4$, R^1 = R^2 = H
3f Ar = 4-BrC$_6$H$_4$, R^1 = R^2 = H
3g Ar = 4-F$_3$CC$_6$H$_4$, R^1 = R^2 = H
3h Ar = 4-NCC$_6$H$_4$, R^1 = R^2 = H
3i Ar = 4-O$_2$NC$_6$H$_4$, R^1 = R^2 = H
3j Ar = 4-MeC$_6$H$_4$, R^1 = R^2 = H
3k Ar = 3-MeC$_6$H$_4$, R^1 = R^2 = H

3l Ar = 2-MeC$_6$H$_4$, R^1 = R^2 = H
3m Ar = 3-ClC$_6$H$_4$, R^1 = R^2 = H
3n Ar = 2-furyl, R^1 = R^2 = H
3o Ar = 2-naphthyl, R^1 = R^2 = H
3p Ar = Ph, R^1 = OMe, R^2 = H
3q Ar = Ph, R^1 = R^2 = Me
3r Ar = Ph, R^1 = Br, R^2 = H
3s Ar = Ph, R^1 = Cl, R^2 = H
3t Ar = Ph, R^1 = H, R^2 = Cl
3u Ar = Ph, R^1 = Ac, R^2 = H

Scheme 1 *Reagents and optimized conditions*: i, **1** (0.1 mmol), **2** (0.2 mmol), CuCl$_2$ (0.02 mmol), TfOH (0.05 mmol), 1,4-dioxane (4 ml), 90 °C, under air, 18 h, sealed tube.

Table 1 Optimization of the reaction conditions.[a]

Entry	[M]	Additive	Solvent	Yield of **3a** (%)[b]
1	Cu(OTf)$_2$	–	1,4-dioxane	31
2	Cu(OTf)$_2$	–	DMF	0
3	Cu(OTf)$_2$	–	MeCN	0
4	AgOTf	–	1,4-dioxane	<5
5	Cu(OAc)$_2$	–	1,4-dioxane	0
6	CuCl$_2$	–	1,4-dioxane	0
7	Cu(OTf)$_2$	TfOH	1,4-dioxane	53, 49[c]
8	Cu(OTf)$_2$	CF$_3$CO$_2$H	1,4-dioxane	0
9	Cu(OTf)$_2$	AcOH	1,4-dioxane	0
10	CuI	TfOH	1,4-dioxane	58
11	CuCl	TfOH	1,4-dioxane	51
12	CuBr$_2$	TfOH	1,4-dioxane	53
13	CuCl$_2$	TfOH	1,4-dioxane	62, 43,[d] 58[e]
14	CuCl$_2$	TfOH	1,4-dioxane	57,[f] 61[g]
15	CuCl$_2$	TfOH	1,4-dioxane	26,[h] 60[i]
16	CuCl$_2$	TfOH	1,4-dioxane	29,[j] 52[k]

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [M] (20 mol%), additive (0.5 equiv.), solvent (4.0 ml), 90 °C, under air, 18 h, sealed tube, unless otherwise noted. [b] Isolated yield. [c] Additive (1.0 equiv.). [d] **1a**/**2a** = 1 : 1. [e] **1a**/**2a** = 1 : 3. [f] Solvent (2.0 ml). [g] Solvent (3.0 ml). [h] Under N$_2$. [i] Under O$_2$. [j] Without CuCl$_2$. [k] CuCl$_2$ (10 mol%).

effect on the product yield, however the substrates with electron-withdrawing groups delivered the desired products somewhat easier than those with electron-donating groups (**3b–c** *vs.* **3d–i**). It is noteworthy that the tolerance of halogens offers an opportunity for further functionalization (compounds **3e**,**f**,**m**,**r–t**). However, the position of the substituents in the aromatic aldehydes significantly affected the reaction yield (**3j–l**), namely, 4-methylbenzaldehyde **1j** produced the relative 2-arylquinoline **3j** in 61% yield, while the use of 2-methylbenzaldehyde **1l** resulted in product **3l** in only 37% yield. Further experiments demonstrated that 2-naphthaldehyde **1o** and furan-2-carbaldehyde **1n** were also good substrates for this reaction as shown for the successful formation of **3n**, **3o** in 65 and 60% yields, respectively. Unfortunately and predictably, aliphatic aldehydes are not suitable for this kind of transformation.

To further explore the scope of the reaction, various arylamines **2a–g** were employed to react with benzaldehyde **1a** and 1,4-dioxane under the optimized conditions. Generally, a series of functional groups, including methyl, methoxy, chloro, bromo and acetyl, were well tolerated thus affording the corresponding products **3p–u** in moderate to good yields. Notably, the electronic properties of the substituent on the benzene ring did affect the reaction outcome, as electron-deficient arylamines gave better results than those with electron-donating substituents. For instance, the reaction of 1-(4-aminophenyl)ethanone **2g** with benzaldehyde **1a** could give the corresponding product **3u** in 62% yield, while the reaction of 4-methoxyaniline **2b** could deliver the desired product **3p** in 39% yield.

Based on the results herein obtained and some relative works,[17] one may propose the following mechanism. Initially, the consideration of benzaldehyde **1** with amine **2** should afford an imine intermediate. The parallel oxidation of 1,4-dioxane may generate unsaturated 2,3-dihydro-1,4-dioxine. After that, the desired quinoline derivatives **3** can be formed upon a double elimination process releasing ethylene glycol as a by-product. The investigation of the mechanism details is still on our lab.

In summary, we have developed a copper-catalyzed three-component coupling sequence for the 2-arylquinolines formation from aldehydes, anilines and 1,4-dioxane. Unexpectedly, 1,4-dioxane served as a C$_2$ building block in this transformation. This formal [4 + 2] approach allows one to rapidly access 2-arylquinolines with broad substrate scope under mild conditions.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.04.028.

[†] *General procedure for the synthesis of* **3a–u**. Under air, aldehyde **1** (0.1 mmol), aniline **2** (0.2 mmol), trifluoromethanesulfonic acid (4.9 µl, 0.05 mmol), CuCl$_2$ (0.02 mmol, 2.69 mg) and 1,4-dioxane (4 ml) were loaded into a 20 ml Schlenk tube equipped with a stirring bar. The sealed Schlenk tube was stirred at 90 °C for about 12 h. After the reaction mixture was cooled to room temperature, it was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel with petroleum ether–ethyl acetate as an eluent to give the desired product **3**.

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